c) **REMARKS**

Courtesies extended to Applicant's representative at the personal interview held February 20, 2003, are acknowledged with appreciation.

The present invention relates generally to methods of determining predisposition of a subject to a mood disorder. Invention methods involve determining the presence of specific kainate receptor subunit GluR7 allelic genotypes or allelic phenotypes. Accordingly, invention methods facilitate diagnosis of predisposition to mood disorder and treatment thereafter.

By the present communication, Table 3 (page 48/49) and Table 4 (page 50) have been amended to clarify that the short hand terms "bipolar I disorder" and "bipolar II disorder" refer to bipolar I depressive disorder and bipolar II depressive disorder, respectively. The specification makes abundantly clear that the invention methods include diagnosis and therapy of depression, and refers in numerous places to bipolar I depressive disorder and bipolar II depressive disorder (see, e.g. ¶¶ 6, 12 and 127). In particular, the text describing Tables 3 and 4 refers to bipolar I and II as depressive disorders. Thus, no new matter is introduced as the amendment merely clarifies a short hand description of a phrase used in the text.

By the present communication, claim 1 has been amended, claims 2-36 have been cancelled, and claims 37-45 have been added. Thus, claims 1 and 37-45 are currently pending. The amendments to Claim 1 and new claims 37-45 are intended to further clarify subject matter that Applicant wishes to pursue in this case. The amendments of the claims find basis in the specification and the originally filed claims. For example, support for claims 44 and 45 is found at ¶ 37 on page 42. Accordingly, there is no issue of new matter.

REJECTION UNDER 35 U.S.C. § 112, FIRST PARAGRAPH

Rejection of claims 1-13 under 35 U.S.C. § 112, first paragraph, as allegedly being based on a non-enabling disclosure is respectfully traversed. The Examiner acknowledges that the specification is enabling for unipolar depressive disorder based on detection of the GluR7 genotype 928 T/T. However, the Examiner asserts that the specification does not reasonably

enable detection of a predisposition of any subject to any mood disorder. It is further alleged that the specification does not reasonably enable detection of a predisposition of a subject to bipolar II depressive disorder based on detection of the GluR7 genotype 928 G/G genotype. Similar allegations have been made with respect to the detection of predisposition based on GluR7 allelic phenotypes.

Although Applicant does not agree with the substance of the rejection, it is noted at the outset that the general concern as to any subject and any mood disorder has been rendered moot by the amended and newly presented claims, which refer to detection of specific human GluR7 genotype or phenotype and to recurrent unipolar or bipolar II depressive disorders. Specific rebuttal to the remaining issues raised in the Office Action follows.

A. The Specification Enables Detection of a GluR7 928 T/T Genotype for Predisposition to Recurrent Unipolar Depressive Disorder.

As mentioned above, the Office Action acknowledges that the specification is enabling for unipolar depressive disorder based on detection of the GluR7 genotype 928 T/T. This is evidenced not only by Table 4, as noted by the Examiner, but also by the text in paragraph 126 (page 47) which shows statistically significant preferential transmission of a GluR7 T-allele from each heterozygous (T/G) parent to offspring affected with recurrent unipolar depressive disorder for 34 of 50 offspring/parent triads analyzed (TDT =6.48; df =1, P =0.011). Accordingly, it must be concluded that claims 1, 40 and 44 are supported by an enabling disclosure.

B. The Specification Enables Detection of a GluR7 G/G Genotype for Predisposition to Bipolar II Depressive Disorder.

The Office Action states that the specification "has not established a correlation between the G/G genotype and the occurrence of bipolar II depressive disorder." The basis offered for this view is the p-value of 1.80 for bipolar II depressive disorder in Table 4 and that the data in Tables 3 and 4 do not necessarily cover bipolar II depressive disorder as opposed to bipolar II disorder (presumably unrelated to depression).

As discussed at the personal interview, Applicants point out that the claims refer to detecting a "predisposition" to bipolar II depressive disorder. Thus, enablement does not require that the method be 100% accurate in predicting whether a subject will get the disease. In addition, the specification makes clear in the text preceding each table that "bipolar II disorder" in the table refers to bipolar II depressive disorder. Accordingly, it must be accepted that all the data in Tables 3 and 4 under the heading bipolar II disorder reflects analysis of bipolar II depressive disorder. However, to avoid any potential confusion, Applicant has amended the specification to eliminate this short hand description.

Finally, although the Examiner emphasizes in the rejection the 1.80 p-value for bipolar II from Table 4 of the specification, Applicant points out that this table reflects all the families tested in aggregate. More relevant is paragraph 126 (page 47/48) which demonstrates a statistically significant preferential transmission of a GluR7 G-allele from each heterozygous (T/G) parent to affected offspring (TDT =5.00; df =1, P =0.025) (a family by family analysis). The claims implicate the more significant data through a requirement that the parents of the subject be heterozygous. Thus, it is concluded that the specification provides reasonable basis to enable detection of a predisposition to bipolar II depressive disorder by detecting a human GluR7 928 G/G genotype inherited from heterozygous parents as recited in claims 38, 42 and 45.

C. The Specification Enables Detection of a Human GluR7 310 Ser/Ser or 310 Ala/Ala Phenotype Associated with Predisposition to Recurrent Unipolar Depressive Disorder and Bipolar II Depressive Disorder, Respectively.

Claims 37 and 41 are directed to detection of a predisposition to recurrent unipolar depressive disorder associated with human GluR7 310 Ser/Ser while claims 39 and 43 are directed to detection of a predisposition to bipolar II depressive disorder associated with human GluR7 310 Ala/Ala. These claims differ from those discussed earlier in that the latter involve analysis of GluR7 phenotype through RNA encoding human GluR7 or the GluR7 protein itself as expressed in neural tissue (e.g., brain). In this regard, the specification provides ample description of phenotype detection methods suitable for GluR7 (see e.g., ¶¶ 39-46). Thus, as the specification demonstrates statistical significance for the underlying genotypic analysis (see above) and provides suitable methods for detecting the expressed allele, it follows that therefore that claims 37, 39, 41, and 43 are supported by an enabling disclosure.

CONCLUSION

In view of the foregoing remarks, prompt and favorable action on all claims is respectfully requested. Should any matters remain outstanding, the Examiner is encouraged to contact the undersigned at the telephone number listed below so that a prompt disposition of this application can be achieved.

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Respectfully submitted,

Date 3/6/03

By _____

Stephen E. Reiter
Attorney for Applicant
Registration No. 31,192

FOLEY & LARDNER
Customer Number: 30542
30542
PATENT TRADEMARK OFFICE
Telephone: (858) 847-6711
Facsimile: (858) 792-6773